REMARKS

Claims 1 to 26 are pending, with the nuclear hormone receptor species RAR and the coactivator species TIF-2/GRIP-1/NCoA-2 and SRC-1/NCoA-1 presently under examination.

Regarding the claim amendments

Claims 1, 11 and 18 have been amended herein to more clearly indicate that, in the claimed methods of identifying an effective agent that dissociates nuclear hormone receptor activities, one assays for corepressor association in the test complex which is increased as compared to corepressor association in a TTNPB-treated control complex when the nuclear hormone receptor is RAR. The amendment to claims 1, 11 and 18 is supported throughout the specification, for example, at page 52, lines 14-19, which indicates that TTNPB treatment of RAR receptor results in release of the corepressor N-CoR, and that an increase in corepressor association in the test complex as compared to TTNPB treated control complex is indicative of corepressor association.

Claims 1, 2, 11 and 18 have been amended herein to more clearly indicate that the recited coactivator association and corepressor association are "in" the test complex. The amendment is supported throughout the specification, for example, at page 11, lines 11-21, which discloses that conditions are provided suitable for forming a test complex

which contains nuclear hormone receptor dimer, coactivator and corepressor.

As set forth above, the amendments are supported in the specification and do not add new matter. The Examiner is therefore respectfully requested to enter the amendments.

Regarding the Rejections under 35 U.S.C. § 112, second paragraph

The rejection of claims 1 to 26 under 35 U.S.C. § 112, second paragraph, as allegedly vague and indefinite is respectfully traversed.

Regarding the term "test complex"

Claims 1 to 26 stand rejected as allegedly vague and indefinite due to recitation of the term "test complex" in independent claims 1, 2, 11 and 18. In this regard, the Examiner asserts that it is not clear whether the coactivator and corepressor are parts of the "test complex" or if the test complex is only receptor dimer.

Applicants submit that the claims are clear and definite to the skilled person in view of the specification and, in particular, that the skilled person understands that the test complex can contain coactivator or corepressor or both. In particular, in view of the specification, the skilled person understands that coactivator or corepressor association or both to nuclear hormone receptor dimers in a test complex is dependent upon the presence and type of ligand. In this regard,

the specification teaches, for example, that the nature of the ligand modulates nuclear hormone receptor interaction with coactivator and corepressor molecules (page 14, lines 23-25) and that certain ligands induce the "simultaneous association" of a coactivator and corepressor to a nuclear hormone receptor (page 9, lines 2-6). Furthermore, the concluding phrase of the independent claims indicates that, where coactivator association is combined with corepressor association, at least one of the agents assayed is an "effective agent," further making clear that whether or not there is coactivator or corepressor association or both depends on the nature of the "one or more agents" with which the nuclear hormone receptor is contacted. From the above, it is clear to the skilled person that the test complex may contain coactivator or corepressor or both. Specifically, the test complex will contain both coactivator and corepressor when the nuclear hormone receptor is contacted with at least one agent which is an "effective agent."

In sum, the claims are clear as written to the skilled person in view of the specification. Accordingly, the Examiner is respectfully requested to reconsider and remove this ground for rejecting claims 1 to 26 under the second paragraph of 35 U.S.C. § 112.

Regarding nuclear hormone receptor "activities"

The claims further stand rejected under the second paragraph of 35 U.S.C. § 112 due to the term "activities" which allegedly is unclear.

Applicants submit that the meaning of nuclear hormone receptor "activities" is clear to the skilled person in view of the specification. As set forth in the specification, nuclear receptor activities include the effects of hormone receptor mediated pathways *indirectly activated* by ligand as well as *direct activation of transcription*. The specification teaches, for example, that ligands that dissociate nuclear hormone receptor activities have selective indirect effects through nuclear hormone receptor-mediated pathways while failing to directly activate transcription through cognate response element (page 9, lines 2-13). The specification further teaches that an effective agent that dissociates nuclear hormone receptor activities has selective activity on an indirect signaling pathway such as an AP-1 or STAT-mediated pathway while lacking or having significantly reduced transcription activity at genes regulated through cognate response elements (page 13, line 22, to page 14, line 8). Thus, the skilled artisan understands that the term "nuclear hormone receptor activities" refers to hormone-mediated biological effects and that this term clearly includes direct (i.e. transcriptional) and indirect biological effects of liganded-nuclear hormone receptor.

In sum, in view of the specification, the phrase "nuclear hormone receptor activities" is clear to one of skill in the art. Applicants therefore respectfully request that the Examiner reconsider and remove this ground for rejection under the second paragraph of 35 U.S.C. § 112.

Regarding the Rejection of Claims 1 to 26 under 35 U.S.C. § 102(b)

The rejection of claims 1 to 26 as allegedly anticipated by DiRenzo et al. under 35 U.S.C. § 102(b) is respectfully traversed. In making the rejection, the Office Action indicates that DiRenzo et al. describe allosteric interactions between RXR and two heterodimeric partners, retinoic acid receptors (RARs) and peroxisome proliferator-activated receptors (PPARs). The Office Action further indicates that DiRenzo et al. determine the effect of TTNPB on recruitment of coactivator (SRC-1) and corepressor (NCoR) to PPAR and RAR (Figure 6, page 2173), alleging that this reference therefore anticipates the invention.

Applicants maintain, for the reasons of record, that claims 1 to 26 are novel over the cited reference. Firstly, the methods of claims 1 to 26 are novel over the PPARγ receptor assays reported in DiRenzo et al. Applicants submit that, at best, Figure 6 of DiRenzo et al. may describe N-CoR (corepressor) association with the PPARγ receptor. However, this reference does not describe analysis of SRC-1 or other coactivator association to the PPARγ receptor. As argued previously, because the claims require assaying a test complex containing nuclear hormone receptor dimer for both coactivator and corepressor association, the claimed methods are novel over the PPARγ assays of the cited reference.

Secondly, the methods of claims 1 to 26 are novel over the RARα assays of DiRenzo et al. As acknowledged by the Examiner and set forth in step (a) of each independent claim, the methods of the invention are practiced by contacting a nuclear hormone receptor with one or more agents "under conditions suitable for forming a test complex comprising nuclear hormone receptor dimer." Thus, the methods of the invention rely on assays in which nuclear hormone receptor homo- or heterodimers are formed. In this regard, RARα is well known to act as a heterodimer with RXR, yet DiRenzo et al. do not supply a source of RXR to the RARα/SRC-1 recruitment assay of Figure 6B. Rather, as indicated in the figure legend, the RARα/SRC-1 recruitment assay is performed using baculovirus-expressed N-CoR, bacterially expressed RARα and in vitro translated SRC-1 without a source of RXR. Applicants maintain that the RARα assay of DiRenzo et al. does not provide conditions suitable for forming an RARα/RXR heterodimer and submit, as discussed further below, that the Figure 6B assay therefore does not show results obtained with "receptor dimer."

In particular, Applicants respectfully disagree with the Examiner's assertion that RARα can form a homodimer, thereby meeting the "nuclear hormone receptor dimer" limitation of the claimed methods. To support the assert that RARs act only as heterodimers, Applicants attach herewith Exhibits A and B. As evidenced in Exhibit A (Nagpal and Chandraratna, Current Pharm. Design 2:295-316 (1996)), RARs do not function as homodimers. See, for example, Exhibit A, page 300, second column, last paragraph, which indicates that RARs are believed to function exclusively *in vivo* as RAR-RXR heterodimers. This assertion is

further corroborated by Exhibit B (Lefebvre, Curr. Drug Targets Immune Endocr. Metabol. Disord.1:153-164 (2001), which states that RARs are active *in vivo* when associated to RXRs (Exhibit B, abstract). Together, these exhibits evidence that a retinoic acid receptor requires a source of RXR in order to dimerize. Given that DiRenzo et al. do not supply a source of RXR, the cited reference does not describe a test complex containing nuclear hormone receptor dimer and, therefore, cannot anticipate the invention.

Regarding corepressor association relative to TTNPB treated control complex

The RAR assays of DiRenzo et al. further cannot anticipate the claimed methods, which as amended indicate that the recited "corepressor association" in a RAR-containing test complex is increased as compared to TTNPB-treated control complex. At best, DiRenzo et al. report the corepressor association observed with TTNPB-treated RAR receptor. Yet DiRenzo et al. do not teach corepressor association which is increased as compared to that observed with TTNPB-treated control complex. Absent such increased corepressor association, the cited reference further cannot anticipate the claimed invention.

In view of the above remarks, Applicants respectfully request that the Examiner reconsider and remove the rejection of claims 1 to 26 under 35 U.S.C. § 102(b) as allegedly anticipated by DiRenzo et al.

Regarding the rejection of claims 1 to 26 under 35 U.S.C. § 103

Applicants respectfully traverse the rejection of claims 1 to 26 under 35 U.S.C. § 103 over DiRenzo et al. The Office Action states that DiRenzo et al. describe a method of determining the effect of an agent (TTNPB) on recruitment of SRC-1 coactivator and N-CoR corepressor to RAR and PPAR and that both coactivator and corepressor are measured. The Office Action asserts that it would have been obvious to practice the methods of the invention with TIF-2 coactivator given the suggestion that members of the SRC-1 family of coactivators such as TIF-2 also may act as coactivators for nuclear hormone receptors.

DiRenzo et al. do not teach or suggest an effective agent that dissociates nuclear hormone receptor activities, or methods suitable for identifying such an agent. As discussed above, an agent that dissociates nuclear hormone receptor activities results in a nuclear hormone-mediated activity without activating transcription through cognate response elements. In contrast, the TTNPB agent used in DiRenzo et al.'s experiments is a known RARα transactivator, i.e. a molecule which activates transcription through RARα cognate response elements (specification at page 10, lines 18-20). Absent a teaching or suggestion of an effective agent that dissociates nuclear hormone receptor activities, the claimed methods are unobvious over the cited reference.

Furthermore, as amended, the methods of the invention are directed to identifying effective agents that result in coactivator association together with corepressor association where, when the nuclear hormone receptor is RAR, the corepressor association is increased as compared to corepressor association in TTNPB-treated control complex. As discussed above, DiRenzo et al. at best describe the effect of TTNPB on recruitment to RARα and focus on differential recruitment to agonist-treated RAR and PPAR. DiRenzo et al. do not provide any motivation to use or identify new ligands that result in corepressor association together with corepressor association to RAR which is increased as compared to that induced by TTNPB. Without any motivation to modify DiRenzo et al. to identify effective agents by assaying for increased corepressor association to RAR as compared to TTNPB, the claimed methods further are unobvious over the cited reference.

In view of the above remarks, Applicants maintain that the claimed methods are unobvious over DiRenzo et al. Accordingly, the Examiner is respectfully requested to remove the rejection of claims 1 to 26 under 35 U.S.C. § 103.

Regarding the Election of Species Requirement

Applicants note the indication that the Election of Species requirement has been made final. Applicants respectfully remind the Examiner that, in the event that a linking claim such as generic claim 1 is found allowable, subject matter directed to non-elected species previously withdrawn from consideration must be rejoined and examined for patentability (MPEP 809).

Respectfully submitted,

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